REMARKS

Reconsideration of this application in view of the above amendments and the following remarks is respectfully requested. Claims 1, 2, 5-8, 10, 12-19 and 35 are now pending. Claims 1, 12-14 and 16 have been amended. Claims 3, 4, 9 and 11 have been canceled. Claims 20-34 have been withdrawn by the Examiner as directed to non-elected subject matter.

As an initial matter, Claim 1 has been redrafted to make the claim more distinct, and thereby overcome the §112 second-paragraph objection, and also to more clearly distinguish claim 1 over the cited prior art. The amendments include the introduction of features of claims 9 and 11, and to recite that the dissociation is monitored in real time by a label-free detection technique (cf. page 7, lines 2-9 of the application). The new claim language is further supported by the disclosure on page 10, lines 10 to 23 of the application, and does not constitute addition of new matter.

In claim 12, the language following the word "preferably" has been deleted. Similarly, in claim 16, the language following the word "preferably" has been deleted, and made the object of a new claim 35. Again, no new matter has been added by way of these amendments.

Prior Art Rejections

The pending claims stand rejected under 35 U.S.C. §103(a) as obvious over the cited prior art references for the reasons of record. Applicants respectfully traverse these rejections for the following reasons.

Conventionally, to determine if two different analytes bind to the same or different binding sites on a multi-site ligand, one of the analytes is labeled, and a mixture of the labeled and unlabeled analyte is contacted with the ligand. A reduction of the detected label when the mixture is contacted with the ligand indicates that the two analytes compete for the same binding site, whereas no reduction indicates that they bind to different sites. In label-free biosensor detection techniques (such as SPR), the total binding interaction at the sensing surface is detected and usually presented as a binding curve having an association part and a dissociation part. As the Examiner will readily appreciate, such convention methodology for determining

binding site specificity cannot be performed with label-free detection, since the individual contributions of the two analytes in the mixture will add to a combined response.

In contrast, and according to the present invention, it has been discovered that a label-free detection technique may be used if (i) the dissociation characteristics of the two analytes differ substantially (*i.e.*, one on the analytes having a substantially faster dissociation than the other), and (ii) the profile (*i.e.*, the shape or appearance) of the dissociation part of a binding curve for the interaction of the analyte mixture with an immobilized ligand is studied. More particularly, the dissociation part (dissociation phase) for the analyte that has the faster dissociation characteristics will (usually) decrease rather rapidly from the equilibrium value to zero or base line, whereas the dissociation phase of the analyte having the slower dissociation characteristics will have a prolonged descent. The dissociation phases of the two analytes are therefore clearly distinguishable from one another.

As a result, if mixtures of the two analytes with successively increased concentrations of the one of the analytes that has the faster dissociation phase are contacted with the ligand to permit association followed by dissociation, the influence of the concentration increase on the dissociation phase for the mixture indicates if the two analytes bind to the same binding site or not. That is, if they bind to the same binding site, the dissociation phase profile will substantially correspond to that of the analyte with the faster binding site alone, as the contribution from the analyte with the slower dissociation phase will gradually disappear. Conversely, the contribution from the analyte with the slower dissociation phase will still be clearly visible if the analytes bind to different binding sites.

The primary reference relied upon by the Examiner (Magali et al., *Molecular Pharmacology*, **36**:405-411) is directed to the use of the conventional label-based competition assay format mentioned above. Specifically, Magali et al. describe experiments with binding of unlabeled antagonists to a muscarinic receptor in the presence of a labeled tracer compound, [^{3}H]NMS, to determine the variation of the apparent receptor specificity with the incubation period in a slowly equilibrating system. Incubations are made for various times up to and including equilibrium. While dissociation kinetics is discussed, no measurements of dissociation are performed.

In sharp contrast, the method of the present invention, which is based on the curve profile of the dissociation phase to determine binding specificity using label-free detection techniques, and is clearly distinguishable from the disclosure of Magali et al. Thus, Magali et al. does not teach or suggest the pending subject matter. Further, the combination of Magali et al. with the various secondary references cited by the Examiner fail to cure this basic deficiency. In other words, Magali et al., taken alone or in any combination with the secondary references cited by the Examiner, does not lead or encourage one skilled in this field to devise the presently claimed invention. Absent such a teaching or motivation, independent claim 1 (as well as claims 2, 5-8, 10 and 35 that depend therefrom) are patentable over the cited references.

In view of the above amendments and remarks, allowance of claims 1, 2, 5-8, 10, 12-19 and 35 is respectfully requested. A good faith effort has been made to place this application in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at (206) 622-4900 to resolve the same.

Respectfully submitted,

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